

REMARKS

This response is filed in reply to the Office Action mailed July 1, 2002. Claims 12, 15, 16, 28, 29, 30 and 36-39 have been canceled. Claims 1, 2-9, 13, 17-20, 23-27, 31-35 and 40-42 have been amended. Support for the amended claims can be found throughout the specification. Claims 1, 2-11, 13, 14, 17-27, 31-35 and 40-42 are pending and at issue. Attached is a marked-up version of the changes being made by the current amendment. Applicant respectfully requests reconsideration of the present application.

Formal Matters

In response to the PTO 948 form, Applicant provides formal drawings with the present response.

Informal Matters

Claim 9 and claims 1, 17, 18, 19, 20, 27, 31, 32 and 33 have been amended to recite, in part, an "E1 gene, E2A gene, E2B gene, E3 gene, E4 gene, E4 promoter, penton gene, fiber gene, hexon gene, or combination thereof."

Claim 15 has been canceled and the limitations of claim 15 have been incorporated into claim 1.

I. REJECTIONS UNDER 35 U.S.C. §112

Written Description

Claims 1-14 and 16-42 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. Applicant notes that this rejection is moot with regard to canceled claims 12, 16, 28, 29, 30 and 36-39. Applicant traverses the pending rejection.

Claims 1, 2-9, 13, 17-20, 23-27, 31-35 and 40-42 have been amended, or depend from a claim that has been amended, to delete the recitation of "having the activity of ..." a 52/55 kDa protein. Applicant believes that the rejection is now moot with regard to the amended claims.

Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph be withdrawn.

II. REJECTIONS UNDER 35 U.S.C. §112

Enablement

Claims 38 and 39 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter not described in the specification in such a way as to enable one of skill in the art to make or use the invention. Applicant submits that this rejection is moot with regard to canceled claim 36-39. Accordingly, Applicant requests that the rejection under 35 U.S.C. §112, first paragraph be withdrawn.

Claims 1-14 and 16-42 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter not described in the specification in such a way as to enable one of skill in the art to make or use the invention. Applicant notes that this rejection is moot with regard to canceled claims 12, 16, 28, 29, 30 and 36-39. Applicants respectfully traverse this rejection as it may apply to the amended claims.

As previously noted, claims 1, 2-9, 13, 17-20, 23-27, 31-35 and 40-42 have been amended, or depend from a claim that has been amended, to delete the recitation of "having the activity of ..." a 52/55 kDa protein. Furthermore, claim 42 has been amended to recite, in part, an "adenovirus" capsid.

Applicant believes that the rejections rejection under 35 U.S.C. §112, first paragraph, are moot with regard to the amended claims. Accordingly, Applicants respectfully request that the rejections be withdrawn.

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CONCLUSION

In summary, for the reasons set forth herein, Applicant maintains that claims 1, 2-11, 13, 14, 17-27, 31-35 and 40-42 clearly and patentably define the invention. Applicant respectfully requests that the Examiner reconsider the various grounds set forth in the Office Action, and allow the claims which are now pending.

If the Examiner would like to discuss any of the issues raised in this response, Applicants' representative can be reached at (858) 678-5070. Please charge any additional fees, or make any credits, to Deposit Account No. 06-1050.

Respectfully submitted,

Date: _____

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Version with markings to show changes made

In the claims:

Claims 12, 15, 16, 28, 29, 30 and 36-39 have been canceled.

Claims 10, 11, 14, 21 and 22 are reiterated for the convenience of the Examiner.

Claims 1, 2-9, 13, 17-20, 23-27, 31-35 and 40-42 have been amended as follows:

1. (Twice Amended) A vector system for selectively packaging a replication defective adenovirus nucleic acid sequence in an adenovirus capsid based on adenovirus serotype, the vector system comprising:
 - (a) a [helper-dependent] first adenovirus nucleic acid sequence comprising:
 - (i) 5' and 3' adenovirus inverted terminal repeats (ITRs);
 - (ii) a[n] first adenovirus serotype-specific cis-acting packaging sequence; and
 - (iii) a heterologous nucleic acid operably linked to a transcriptional control sequence;
 - (b) a [helper] second adenovirus nucleic acid sequence comprising:
 - (i) 5' and 3' adenovirus ITRs;
 - (ii) a[n] second adenovirus serotype-specific cis-acting packaging sequence, wherein the [helper] second adenovirus nucleic acid fails to [produce a polypeptide having the activity of the helper adenovirus serotype] encode a 52/55 kDa trans-acting protein specific for the second cis-acting packaging sequence; and
 - (c) [a polypeptide having activity of] a 52/55 kDa trans-acting protein that supports packaging of the [helper-dependent] first adenovirus nucleic acid sequence and fails to support packaging of the [helper] second adenovirus nucleic acid sequence, wherein the replication defective adenovirus comprises a defective or modified adenovirus E1 gene, E2A gene, E2B gene, E3 gene, E4 gene, E4 promoter, [a] penton gene, [a] fiber gene, [or a] hexon gene, or a combination thereof.
2. (Amended) The vector system of claim 1, wherein the adenovirus capsid, packaging and 52/55 kDa [*trans*-acting] protein encoding sequences are human adenovirus sequences.

3. (Twice Amended) The vector system of claim [2] 1, wherein the [helper-dependent] first and [helper] second adenovirus serotype[s]-specific cis-acting packaging sequences are selected from the group consisting of adenovirus type 2 (Ad2), adenovirus type 5 (Ad5), adenovirus type 7 (Ad7), adenovirus type 12 (Ad12), adenovirus type 17 (Ad17), and adenovirus type 40 (Ad40) packaging sequences.
4. (Twice Amended) The vector system of claim [2] 3, wherein the [helper-dependent] first adenovirus serotype-specific cis-acting packaging sequence is from adenovirus type 5 and the [helper] second adenovirus serotype-specific cis-acting packaging sequence is from adenovirus type 7.
5. (Twice Amended) The vector system of claim [2] 3, wherein the [helper-dependent] first adenovirus serotype-specific cis-acting packaging sequence is from adenovirus type 7 and the [helper] second adenovirus serotype-specific cis-acting packaging sequence is from adenovirus type 5.
6. (Twice Amended) The vector system of claim 1, wherein the [helper-dependent] first adenovirus nucleic acid sequence fails to produce a complete adenovirus capsid.
7. (Twice Amended) The vector system of claim 6, wherein the [helper-dependent] first adenovirus sequence is encapsidated in a capsid comprising at least one polypeptide encoded by the [helper] second adenovirus sequence.
8. (Twice Amended) The vector system of claim 6, wherein the [helper-dependent] first adenovirus sequence is packaged in a capsid encoded by the [helper] second adenovirus sequence.
9. (Twice Amended) The vector system of claim 42, wherein the replication defective adenovirus comprises a defective or modified adenovirus E1 gene, E2A gene, E2B gene, E3 gene, E4 gene, E4 promoter, penton gene, fiber gene, [or] hexon gene or combination thereof.

10. (Reiterated) The vector system of claim 1, wherein the failure to produce a functional 52/55 kDa trans-acting protein is due to a mutation in the sequence encoding the protein.
11. (Reiterated) The vector system of claim 10, wherein the mutation is a missense mutation, a point mutation, a frameshift mutation or a deletion mutation.
12. (Canceled) The vector system of claim 1, wherein the helper adenovirus sequence further comprises a nucleic acid sequence encoding the polypeptide having the activity of the 52/55 kDa trans-acting protein that supports packaging of the helper-dependent adenovirus nucleic acid.
13. (Twice Amended) The vector system of claim 1, wherein the [polypeptide having the activity of the] 52/55 kDa trans-acting protein that supports packaging of the helper-dependent adenovirus nucleic acid sequence is encoded by a nucleic acid sequence functionally-associated with the genome of an adenovirus replication competent host cell.
14. (Reiterated) The vector system of claim 13, wherein adenovirus replication competent host cell is a 293 cell line.
15. (Canceled) The vector system of claim 1, wherein the polypeptide having the activity of a 52/55 kDa trans-acting protein that supports packaging of the helper-dependent adenovirus nucleic acid sequence is a 52/55 kDa trans-acting protein.
16. (Canceled) The vector system of claim 1, wherein the helper-dependent adenovirus sequence lacks at least one nucleic acid sequence needed to produce a capsid and further comprises a nucleic acid sequence encoding a polypeptide having the activity of a 52/55 kDa trans-acting protein that supports packaging of the helper-dependent adenovirus nucleic acid sequence.

17. (Twice Amended) A vector system for selectively packaging a replication defective adenovirus nucleic acid sequence in an adenovirus capsid based on adenovirus serotype, the vector system comprising:

- (a) a [helper-dependent] first adenovirus nucleic acid sequence comprising:
 - (i) 5' and 3' adenovirus ITRs;
 - (ii) a[n] first adenovirus serotype-specific cis-acting packaging sequence; and
 - (iii) a heterologous nucleic acid operably linked to a transcriptional control sequence;
- (b) a [helper] second adenovirus nucleic acid sequence comprising:
 - (i) 5' and 3' adenovirus ITRs;
 - (ii) a[n] second adenovirus serotype-specific cis-acting packaging sequence; and
 - (iii) a nucleic acid sequence encoding a [polypeptide having the activity of a] 52/55 kDa trans-acting protein that supports packaging of the [helper-dependent] first adenovirus nucleic acid sequence and fails to support packaging of the [helper] second adenovirus nucleic acid sequence,

wherein the replication defective adenovirus comprises a defective or modified adenovirus E1 gene, E2A gene, E2B gene, E3 gene, E4 gene, E4 promoter, [a] penton gene, [a] fiber gene, [or a] hexon gene, or a combination thereof.

18. (Twice Amended) A vector system for selectively packaging a replication defective adenovirus nucleic acid sequence in an adenovirus capsid based on adenovirus serotype, the vector system comprising:

- (a) a [helper-dependent] first adenovirus nucleic acid sequence comprising:
 - (i) 5' and 3' adenovirus ITRs;
 - (ii) a[n] first adenovirus serotype-specific cis-acting packaging sequence; and
 - (iii) a heterologous nucleic acid operably linked to a transcriptional control sequence;
- b) a [helper] second adenovirus nucleic acid sequence comprising:
 - (i) 5' and 3' adenovirus ITRs;
 - (ii) a[n] second adenovirus serotype-specific cis-acting packaging sequence,

wherein the [helper] second adenovirus nucleic acid fails to [produce] encode a [polypeptide having the activity of the helper adenovirus serotype] 52/55 kDa [trans-acting] protein specific for the second cis-acting packaging sequence; and

(c) a cell comprising a nucleic acid sequence encoding [a polypeptide having the activity of a helper-dependent] adenovirus serotype 52/55 kDa trans-acting protein specific for the first cis-acting packaging sequence,

wherein the replication defective adenovirus comprises a defective or modified adenovirus E1 gene, E2A gene, E2B gene, E3 gene, E4 gene, E4 promoter, [a] penton gene, [a] fiber gene, [or a] hexon gene, or a combination thereof.

19. (Twice Amended) A vector system for selectively packaging a replication defective adenovirus nucleic acid sequence in an adenovirus capsid based on adenovirus serotype, the vector system comprising:

(a) a [helper-dependent] first adenovirus nucleic acid sequence comprising:

(i) 5' and 3' adenovirus ITRs;

(ii) a[n] first adenovirus serotype-specific cis-acting packaging sequence; and

(iii) a heterologous nucleic acid operably linked to a transcriptional control sequence;

(b) a [helper] second adenovirus nucleic acid sequence comprising:

(i) 5' and 3' adenovirus ITRs;

(ii) a[n] second adenovirus serotype-specific cis-acting packaging sequence,

wherein the helper adenovirus nucleic acid fails to [produce] encode a polypeptide having the activity of the helper adenovirus serotype 52/55 kDa trans-acting protein; and

(c) an expression cassette comprising a nucleic acid sequence encoding [a polypeptide having the activity of a helper-dependent] adenovirus serotype 52/55 kDa trans-acting protein specific for a first adenovirus serotype-specific cis-acting packaging sequence,

wherein the replication defective adenovirus comprises a defective or modified adenovirus E1 gene, E2A gene, E2B gene, E3 gene, E4 gene, E4 promoter, [a] penton gene, [a] fiber gene, [or a] hexon gene, or a combination thereof.

20. (Twice Amended) A vector comprising a replication defective adenovirus sequence comprising:

- (a) a [helper-dependent] first adenovirus serotype-specific cis-acting packaging sequence; and
- (b) a nucleic acid sequence encoding a functional [helper] second adenovirus serotype-specific 52/55 kDa [trans-acting] protein, wherein [the helper adenovirus serotype 52/55 kDa trans-acting] said protein is not specific for the first adenovirus serotype-specific cis-acting packaging sequence [does not have the activity of a helper-dependent adenovirus serotype 52/55 kDa trans-acting protein, lacking the ability to produce a polypeptide having the activity of a helper-dependent adenovirus serotype 52/55 kDa trans-acting protein],

wherein the replication defective adenovirus sequence comprises a defective or modified adenovirus E1 gene, E2A gene, E2B gene, E3 gene, E4 gene, E4 promoter, [a] penton gene, [a] fiber gene, [or a] hexon gene, or a combination thereof.

21. (Reiterated) The vector of claim 20, further comprising at least one adenoviral nucleic acid sequence needed to produce an adenoviral capsid.

22. (Reiterated) The vector of claim 21, further comprising sufficient adenoviral nucleic acid sequence to produce a complete adenoviral capsid when the vector is expressed in an adenovirus replication-competent host cell.

23. (Twice Amended) The vector of claim 20, wherein the [helper-dependent] first adenovirus serotype-specific cis-acting packaging sequence and [helper] second adenovirus serotype[s]-specific a nucleic acid sequence are selected from the group consisting of adenovirus type 2 (Ad2), adenovirus type 5 (Ad5), adenovirus type 7 (Ad7), adenovirus type 12 (Ad12), adenovirus type 17 (Ad17), and adenovirus type 40 (Ad40).

24. (Twice Amended) The vector of claim 23, wherein the [helper-dependent] first adenovirus serotype sequence is adenovirus type 5 and the [helper] second adenovirus serotype sequence is adenovirus type 7.

25. (Twice Amended) The vector of claim 23, wherein the [helper-dependent] first adenovirus serotype sequence is adenovirus type 7 and the [helper] second adenovirus serotype sequence is adenovirus type 5.

26. (Amended) A transformed or isolated infected cell comprising the vector system of claim 1, claim 17, claim 18, claim 19 or the vector of claim 20.

27. (Twice Amended) A kit useful for making adenovirus encapsidated replication defective nucleic acid sequences comprising carrier means being compartmentalized to receive in close confinement therein one or more containers comprising a vector system of claim 1, claim 17, claim 18 or claim 19 [:

- (a) a helper-dependent adenovirus nucleic acid sequence comprising:
 - (i) 5' and 3' adenovirus inverted terminal repeats (ITRs);
 - (ii) an adenovirus serotype-specific cis-acting packaging sequence; and
 - (iii) a heterologous nucleic acid;
- (b) a helper adenovirus nucleic acid sequence comprising:
 - (i) 5' and 3' adenovirus ITRs;
 - (ii) an adenovirus serotype-specific cis-acting packaging sequence, wherein the helper adenovirus nucleic acid fails to produce a polypeptide having the activity of the helper adenovirus serotype 52/55 kDa trans-acting protein; and
- (c) a nucleic acid sequence encoding a polypeptide having the activity of a helper-dependent adenovirus serotype 52/55 kDa trans-acting protein,
wherein the replication defective adenovirus comprises a defective or modified adenovirus E1 gene, E2A gene, E2B gene, E3 gene, E4 gene, E4 promoter, a penton gene, a fiber gene or a hexon gene, or a combination thereof].

28. (Canceled) The kit of claim 27, wherein the polypeptide having the activity of the 52/55 kDa trans-acting protein that supports packaging of the helper-dependent adenovirus nucleic acid

sequence is encoded by a nucleic acid sequence functionally-associated with the genome of an adenovirus replication competent host cell.

29. (Canceled) The kit of claim 27, wherein the nucleic acid sequence encoding a polypeptide having the activity of a helper-dependent adenovirus serotype 52/55 kDa trans-acting protein further comprises an expression cassette.

30. (Canceled) The kit of claim 27, wherein the helper adenovirus sequence further comprises the nucleic acid sequence encoding a polypeptide having the activity of a helper-dependent adenovirus serotype 52/55 kDa trans-acting protein.

31. (Twice Amended) A method of producing a replication defective encapsidated adenovirus [gene transfer] vector, comprising the following steps:

(a) transforming or infecting into adenovirus replication competent host cells

(i) a [helper-dependent] first adenovirus nucleic acid sequence comprising:

5' and 3' adenovirus inverted terminal repeats (ITRs);

a[n] first adenovirus serotype-specific cis-acting packaging sequence; and

a heterologous gene operably linked to a transcriptional control sequence;

(ii) a [helper] second adenovirus nucleic acid sequence comprising:

5' and 3' adenovirus ITRs;

a[n] second adenovirus serotype-specific cis-acting packaging sequence,

wherein the [helper] second adenovirus nucleic acid fails to [produce] encode a [polypeptide having the activity of the helper adenovirus serotype] 52/55 kDa [trans-acting] protein specific for the second adenovirus serotype-specific cis-acting packaging sequence; and

(iii) a nucleic acid sequence encoding a [polypeptide having the activity of a] 52/55 kDa [trans-acting] protein specific for a first adenovirus serotype-specific cis-acting packaging sequence [that supports packaging of the helper-dependent adenovirus nucleic acid sequence and fails to support packaging of the helper adenovirus nucleic acid sequence]; and

(b) culturing the cells under conditions where the [helper-dependent] first replication defective adenovirus sequence is encapsidated to produce a replication defective adenovirus [gene transfer] vector,

wherein the replication defective adenovirus comprises a defective or modified adenovirus E1 gene, E2A gene, E2B gene, E3 gene, E4 gene, E4 promoter, [a] penton gene, [a] fiber gene, [or a] hexon gene, or a combination thereof.

32. (Twice Amended) A method of producing a replication defective encapsidated adenovirus [gene transfer] vector, comprising the following steps:

(a) transforming or infecting into an adenovirus replication competent host cell a first and second [two] adenovirus replication defective sequences, wherein the cell comprises a nucleic acid sequence encoding a [polypeptide having the activity of an adenovirus serotype] 52/55 kDa trans-acting protein that supports packaging of a [helper-dependent] first adenovirus nucleic acid sequence and fails to support packaging of a [helper] second adenovirus nucleic acid sequence, and wherein

(i) [a helper-dependent] the first adenovirus nucleic acid sequence compris[ing]es:

5' and 3' adenovirus inverted terminal repeats (ITRs);

a[n] first adenovirus serotype-specific cis-acting packaging sequence; and

a heterologous gene operably linked to a transcriptional control sequence;

(ii) [a helper] the second adenovirus nucleic acid sequence compris[ing]es:

5' and 3' adenovirus ITRs;

a[n] second adenovirus serotype-specific cis-acting packaging sequence,

wherein the [helper] second adenovirus nucleic acid fails to [produce] encode a [polypeptide having the activity of the helper adenovirus serotype] 52/55 kDa trans-acting protein specific for the second adenovirus serotype-specific cis-acting packaging sequence; and
(b) culturing the cells under conditions where the [helper-dependent] first replication defective adenovirus sequence is encapsidated to produce a replication defective adenovirus [gene transfer] vector,

wherein the replication defective adenovirus comprises a defective or modified adenovirus E1 gene, E2A gene, E2B gene, E3 gene, E4 gene, E4 promoter, [a] penton gene, [a] fiber gene, [or a] hexon gene, or a combination thereof.

33. (Twice Amended) A method of producing a replication defective encapsidated adenovirus [gene transfer] vector, comprising the following steps:

(a) transforming or infecting a first and second [two] adenovirus replication defective sequences into an adenovirus replication competent host cell, wherein [the two sequences comprise:]

(i) [a helper-dependent] the first adenovirus nucleic acid sequence compris[ing]es:

5' and 3' adenovirus inverted terminal repeats (ITRs);

a[n] first adenovirus serotype-specific cis-acting packaging sequence;

a heterologous gene operably linked to a transcriptional control sequence; and

a nucleic acid sequence encoding a [polypeptide having the activity of a] 52/55 kDa [trans-acting] protein specific for the first adenovirus serotype-specific cis-acting packaging sequence [that supports packaging of the helper-dependent adenovirus nucleic acid sequence and fails to support packaging of the helper adenovirus nucleic acid sequence]; and

(ii) [a helper] the second adenovirus nucleic acid sequence compris[ing]es:

5' and 3' adenovirus ITRs;

a[n] second adenovirus serotype-specific cis-acting packaging sequence,

wherein the [helper] second adenovirus nucleic acid fails to [produce] encode a [polypeptide having the activity of the helper adenovirus serotype] 52/55 kDa trans-acting protein specific for the second adenovirus serotype-specific cis-acting packaging sequence; and

(b) culturing the cells under conditions where the [helper-dependent] first replication defective adenovirus sequence is encapsidated to produce a replication defective adenovirus [gene transfer] vector,

wherein the replication defective adenovirus comprises a defective or modified adenovirus E1 gene, E2A gene, E2B gene, E3 gene, E4 gene, E4 promoter, [a] penton gene, [a] fiber gene, [or a] hexon gene, or a combination thereof.

34. (Twice Amended) The method of claim 31, 32, or 33 wherein the [helper] second adenovirus sequence further comprises an adenoviral nucleic acid sequence encoding a complete adenoviral viral capsid.

35. (Twice Amended) A vector for selectively packaging replication defective nucleic acid sequences in adenovirus capsids, the vector comprising:

- (a) a replication defective adenovirus sequence comprising an adenovirus serotype 7 (Ad7) cis-acting packaging sequence;
- (b) a nucleic acid sequence encoding [a polypeptide having the activity of] an adenovirus serotype 5 (Ad5) 52/55 kDa [trans-acting] protein; and
- (c) an adenoviral nucleic acid sequence that encodes a viral capsid and fails to encode or produce [a polypeptide having the activity of] an adenovirus 7 serotype 52/55 kDa trans-acting protein.

36. (Canceled) A pharmaceutical composition comprising an encapsidated replication defective adenovirus, made using the vector system of claim 1, substantially free of helper virus, and a pharmaceutically acceptable excipient.

37. (Canceled) The pharmaceutical composition of claim 36, wherein the pharmaceutical composition is 99% free of helper virus.

38. (Canceled) A method of delivering a heterologous nucleic acid to cell comprising transforming or infecting a cell with the pharmaceutical composition of claim 36.

39. (Canceled) The method of claim 38, wherein the pharmaceutical composition is administered to a patient systemically, regionally or locally.

40. (Amended) A packaging cell line for selectively packaging a replication defective adenovirus nucleic acid sequence in an adenovirus capsid, the cell line comprising:

- (a) a [helper-dependent] first adenovirus nucleic acid sequence comprising:

- (i) 5' and 3' adenovirus inverted terminal repeats (ITRs);
 - (ii) a[n] first adenovirus serotype-specific cis-acting packaging sequence; and
 - (iii) a heterologous nucleic acid operably linked to a transcriptional control sequence;
- (b) a [helper] second adenovirus nucleic acid sequence comprising:
- (i) 5' and 3' adenovirus ITRs;
 - (ii) a[n] second adenovirus serotype-specific cis-acting packaging sequence,
- wherein the [helper] second adenovirus nucleic acid fails to [produce] encode a [polypeptide having the activity of the helper adenovirus serotype] 52/55 kDa trans-acting protein specific for the second adenovirus serotype-specific cis-acting packaging sequence; and
- (c) [a polypeptide having activity of] a 52/55 kDa trans-acting protein specific for the first adenovirus serotype-specific cis-acting packaging sequence [that supports packaging of the helper-dependent adenovirus nucleic acid sequence and fails to support packaging of the helper adenovirus nucleic acid sequence],

wherein the replication defective adenovirus comprises a defective or modified adenovirus E1 gene, E2A gene, E2B gene, E3 gene, E4 gene, E4 promoter, [a] penton gene, [a] fiber gene, [or a] hexon gene, or a combination thereof.

41. (Amended) A packaging cell line for selectively packaging a replication defective adenovirus nucleic acid sequence in an adenovirus capsid, the cell line comprising:
- (a) a nucleic acid sequence encoding [a polypeptide having the activity of] an adenovirus serotype-specific 52/55 kDa trans-acting protein;
 - (b) a [helper-dependent] first adenovirus nucleic acid sequence comprising:
 - (i) 5' and 3' adenovirus inverted terminal repeats (ITRs);
 - (ii) a[n] first adenovirus serotype-specific cis-acting packaging sequence; and
 - (iii) a heterologous nucleic acid operably linked to a transcriptional control sequence;
 - (c) a [helper] second adenovirus nucleic acid sequence comprising:
 - (i) 5' and 3' adenovirus ITRs;
 - (ii) a[n] second adenovirus serotype-specific cis-acting packaging sequence that fails to support the activity of the [polypeptide having the activity of an adenovirus] serotype-specific 52/55 kDa trans-acting protein,

wherein the replication defective adenovirus comprises a defective or modified adenovirus E1 gene, E2A gene, E2B gene, E3 gene, E4 gene, E4 promoter, [a] penton gene, [a] fiber gene, [or a] hexon gene, or a combination thereof.

42. (Amended) A vector system for selectively packaging a replication defective nucleic acid sequence in an adenovirus capsid, the vector system comprising:

(a) a [helper-dependent] first adenovirus nucleic acid sequence comprising:

- (i) 5' and 3' viral inverted terminal repeats (ITRs);
- (ii) a first adenovirus serotype-specific cis-acting packaging sequence; and
- (iii) a heterologous nucleic acid operably linked to a transcriptional control sequence,

wherein the [helper-dependent] first adenovirus nucleic acid fails to produce a [polypeptide having the activity of a serotype-specific] 52/55 kDa trans-acting protein specific for the first adenovirus serotype-specific cis-acting packaging sequence;

(b) a [helper] second adenovirus nucleic acid sequence comprising:

- (i) 5' and 3' virus ITRs;
- (ii) a second adenovirus serotype-specific cis-acting packaging sequence,

wherein the [helper] second adenovirus nucleic acid fails to produce a [polypeptide having the activity of a serotype-specific] 52/55 kDa trans-acting protein specific for the second adenovirus serotype-specific cis-acting packaging sequence; and

(c) a nucleic acid encoding a [polypeptide or a polypeptide having an activity of a] serotype-specific 52/55 kDa trans-acting protein that supports packaging of the first adenovirus serotype-specific cis-acting packaging sequence and fails to support packaging of the second adenovirus serotype-specific cis-acting packaging sequence.